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FILE 'USPAT' ENTERED AT 18:13:54 ON 18 MAY 1998

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 *              W E L C O M E   T O   T H E                    *
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=> e cobbold/in

E#      FILE            FREQUENCY  TERM
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E1      USPAT                2     COBBLEDICK, DAVID STANLEY/IN
E2      USPAT                2     COBBLEY, DAVID A/IN
E3      USPAT                0 --> COBBOLD/IN
E4      USPAT                1     COBBOLD, STEPHEN P/IN
E5      USPAT                1     COBBOLD, STEPHEN PAUL/IN
E6      USPAT                1     COBBS, CARRINGTON S/IN
E7      USPAT                1     COBBS, DAVID/IN
E8      USPAT                3     COBBS, DAVID C/IN
E9      USPAT                1     COBBS, DAVID H/IN
E10     USPAT               12     COBBS, JAMES H/IN
E11     USPAT                7     COBBS, KEITH E/IN
E12     USPAT                1     COBBS, RICHARD W/IN

=> s e4,e5

             1 "COBBOLD, STEPHEN P"/IN
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              1 "COBBOLD, STEPHEN PAUL"/IN
L1            2 ("COBBOLD, STEPHEN P"/IN OR "COBBOLD, STEPHEN PAUL"/IN)

=> d l1 1-2
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1. 5,690,933, Nov. 25, 1997, Monoclonal antibodies for inducing tolerance; **Stephen Paul Cobbold**, et al., 424/144.1, 143.1, 153.1, 154.1, 173.1; 514/11 [IMAGE AVAILABLE]

2. 4,841,025, Jun. 20, 1989, Antibody preparations; **Stephen P. Cobbold**, et al., 530/387.3; 424/133.1, 141.1, 154.1, 155.1; 530/388.1, 388.2, 388.7, 388.75, 388.8, 412, 413, 808; 935/107, 110 [IMAGE AVAILABLE]

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=> s (non(w)deplet? or nondeplet?)(P)(antibod? or immunoglobulin?)

        831670 NON
         48710 DEPLET?
            74 NONDEPLET?
         28008 ANTIBOD?
          8532 IMMUNOGLOBULIN?
L2           7 (NON(W)DEPLET? OR NONDEPLET?)(P)(ANTIBOD? OR IMMUNOGLOBULIN
?)

=> d l2 1-7
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1. 5,690,933, Nov. 25, 1997, Monoclonal antibodies for inducing tolerance; Stephen Paul Cobbold, et al., 424/144.1, 143.1, 153.1, 154.1, 173.1; 514/11 [IMAGE AVAILABLE]

2. 5,670,150, Sep. 23, 1997, **Non-depleting** CD4-specific monoclonal **antibodies** for the treatment of insulin-dependent diabetes mellitus (IDDM); Anne Cooke, et al., 424/154.1, 143.1, 145.1, 158.1; 530/388.24, 388.75 [IMAGE AVAILABLE]

3. 5,635,156, Jun. 3, 1997, Non-lethal methods for conditioning a recipient for bone marrow transplantation; Suzanne T. Ildstad, 424/1.49, 130.1, 141.1, 152.1, 153.1, 154.1, 178.1, 181.1, 183.1; 600/1; 604/20 [IMAGE AVAILABLE]

4. 5,603,958, Feb. 18, 1997, Pharmaceutical carrier; Bror Morein, et al., 424/489, 484 [IMAGE AVAILABLE]

5. 5,514,364, May 7, 1996, Non-lethal methods for conditioning a recipient for bone marrow transplantation; Suzanne T. Ildstad, 424/1.49, 130.1, 141.1, 152.1, 153.1, 154.1, 178.1, 183.1; 600/1; 604/20 [IMAGE AVAILABLE]

6. 5,229,275, Jul. 20, 1993, In-vitro method for producing antigen-specific human monoclonal antibodies; Diana K. Goroff, 435/70.1; 424/85.2; 435/70.21, 70.4; 530/351, 387.1, 388.1 [IMAGE AVAILABLE]

7. 4,971,801, Nov. 20, 1990, Biologic response modifier; Richard W. Urban, 424/450; 264/4.3; 424/85.2, 282.1; 428/402.2; 436/829; 514/885 [IMAGE AVAILABLE]

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=> d l2 1-7 kwic
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US PAT NO: 5,690,933 [IMAGE AVAILABLE] L2: 1 of 7

ABSTRACT:
Tolerance to an antigen is induced in a subject by administering a

non-depleting CD4 monoclonal **antibody** and a **non-depleting** CD8 monoclonal **antibody**. Tolerance to the antigen can be induced under cover of these **antibodies**. A depleting CD4 monoclonal **antibody** and/or a depicting CD8 monoclonal **antibody** may be administered prior to the **non-depleting antibodies**.

SUMMARY:

BSUM(5)

Previous studies have used **antibodies** that deplete CD4 cells. We have now found that **non-depleting** CD4 and CD8 **antibodies** can also produce tolerance to foreign **immunoglobulins**, bone marrow and skin grafts. Indeed, this observation has general applicability to all antigens. Further, we have found that administration of a depleting CD4 mAb and/or a depleting CD8 mAb prior to administration of the **non-depleting** mAbs can be beneficial in creating a tolerance-permissive environment.

SUMMARY:

BSUM(15)

A combination of **non-depleting** CD4 and CD8 mAbs can be used to induce tolerance to any antigen without the need for other immunosuppressive agents. A **non-depleting** mAb is a mAb which depletes fewer than 50%, for example from 10 to 25% and preferably less than 10%. . . . presented. Apart from transplantation antigens, the present invention can be used to induce tolerance to globular proteins, glycoproteins such as **immunoglobulins**, materials carried on particles such as pollen proteins, polypeptides intended for therapeutic use such as interferon, interleukin-2 or tumour necrosis. . .

SUMMARY:

BSUM(17)

The . . . example three times a week, for from 2 to 4 weeks, preferably for 3 weeks. An effective amount of the **non-depleting** mAbs is given. Testing for saturating amounts of **antibody** in serum should indicate that sufficient **antibody** is present. Enough of each **non-depleting** mAb is consequently administered to induce a tolerance-permissive environment in a subject under treatment. The CD4 and CD8 cells can. . .

SUMMARY:

BSUM(18)

The amount of **non-depleting** CD4 mAb and of **non-depleting** CD8 mAb administered to a patient depends upon a variety of factors including the age and weight of a patient,. . . from 1 to 400 mg, such as from 3 to 30 mg, for example from 5 to 20 mg, of **antibody** may be given. A CD11a mAb, a **non-depleting** mAb, may be used in addition to CD4 and CD8 mAbs or in place of either or both of the. . .

SUMMARY:

BSUM(22)

It . . . be preferable to treat a host with a depleting CD4 mAb and/or a depleting CD8 mAb before commencing treatment with **non-depleting** mAbs. A depleting mAb is a mAb which depletes more than 50%, for example from 90 to 99%, of target cells in vivo. Depleting

antibodies include rat IgG.sub.2b or IgG.sub.1, mouse IgG.sub.2a and human IgG.sub.1 and IgG.sub.3. A depleting CD4 mAb and/or a depleting CD8 mAb may therefore be used to reduce the relevant population of T cells. The **non-depleting** mAbs therefore have fewer T cells to work on. Depletion may alternatively be achieved by conventional immunosuppressive therapy such as. . .

SUMMARY:

BSUM(25)

The . . . preferably once, from 1 to 7 days, for example from 1 to 5 days, before commencement of the treatment with **non-depleting** CD4 and CD8 mAbs. An antigen to which it is desired to induce tolerance may be administered at the same. . . from 1 to 400 mg, such as from 3 to 30 mg, for example from 5 to 20 mg, of **antibody** may be given.

SUMMARY:

BSUM(26)

The depleting and **non-depleting** CD4 and CD8 mAbs can be raised in any convenient manner. They may be made by conventional methods of fusing. . . rat spleen cells to a rat myeloma cell line such as Y3/Ag 1.2.3. (Clark and Waldmann, chapter 1 of "Monoclonal **Antibodies**", which is a book edited by P. C. L. Beverley in a series "Methods in Hematology", Longman (Churchill Livingstone), 1986).. . .

DETDESC:

DETD(72)

Example 1 has shown that three weeks of therapy with **non-depleting** CD4 and CD8 **antibodies** permitted tolerance to multiple minor incompatible skin grafts. In order to establish a treatment protocol that might tolerize across strong MHC differences we compared the effects of administering depleting (rat IgG2b), **non-depleting** (blocking rat IgG2a) and a combination of depleting followed by blocking CD4 and CD8 **antibodies** to CBA/Ca (H-2.sup.k) mice grafted with BALB/c (H-2.sup.d) skin (FIG. 9). As we have previously reported, a strictly depleting protocol delayed rejection significantly, but all mice rejected within 70 days (MST=55 days). **Non-depleting** **antibodies** were here less effective (MST=28 days), but a combination of two depleting doses followed by blockade with rat IgG2a **antibodies** gave the longest graft survival (MST>100 days), although most (but not all) grafts were rejected by 200 days. In this. . .

DETDESC:

DETD(80)

One mechanism for the suppression of graft rejection by **non-depleting** monoclonal **antibodies** is through blocking the function of CD4 and CD8 accessory molecules on the T-cell surface during antigen presentation. This would be most effective only if serum **antibody** was maintained at levels sufficient to saturate antigen positive cells. The levels of active **antibody** in treated mice was indeed found to be sufficient to saturate the target CD4 and CD8 antigens throughout the three weeks of treatment, and in some mice up to three weeks after stopping **antibody** administration (Table 8). However, by day 60, there was no detectable (<0.5 ng/ml CD4 and <10 ng/ml CD8) monoclonal **antibody** left in the serum which could otherwise have maintained a non-specific immunosuppression. It should be noted that none of the. . . antiglobulin (neither anti-species nor anti-idiotype) as measured by a capture ELISA, indicating that mice were also rendered

tolerant of rat **immunoglobulin** by this protocol.

DETDESC:

DETD(87)

The . . . experiment, combined depletion followed by blockade was most effective (FIG. 13a), but as 3/6 of the mice given the blocking (**non-depleting**) **antibodies** also held their second grafts (FIG. 13b), it must be possible even for effector T-cells to be rendered inactive or. . .

CLAIMS:

CLMS(1)

We . . .

reaction to a self-antigen, said method comprising administering to a human in need of said treatment an amount of a **non-depleting** anti-CD4 monoclonal **antibody** as the whole **antibody** sufficient to induce long-term specific immunological unresponsiveness to said self-antigen thereby effecting said treatment.

US PAT NO: 5,670,150 [IMAGE AVAILABLE] L2: 2 of 7
TITLE: **Non-depleting** CD4-specific monoclonal **antibodies** for the treatment of insulin-dependent diabetes mellitus (IDDM)

ABSTRACT:
Non-depleting CD4 monoclonal **antibodies** may be used in the treatment of insulin-dependent diabetes mellitus.

SUMMARY:

BSUM(4)

The present invention is founded upon the surprising observation that administration of a **non-depleting** CD4 monoclonal **antibody** (hereafter nd CD4 mAb) can arrest the loss of insulin-producing cells in an animal model of IDDM. It is now. . .

SUMMARY:

BSUM(5)

WO-A-90/15152 describes the use of nd CD4 mAbs in conjunction with **non-depleting** CD8 monoclonal **antibodies** in inducing tolerance to an antigen and suggests that this may be useful in surgery and therapy, for instance in. . .

SUMMARY:

BSUM(6)

Accordingly . . . present invention provides a method for treating insulin-dependant diabetes mellitus comprising administering an effective, non-toxic amount of at least one **non-depleting** CD4 monoclonal **antibody** to a human or non-human patient in need thereof.

SUMMARY:

BSUM(9)

As used herein the term "**non-depleting** CD4 monoclonal

antibody" refers to CD4 monoclonal **antibodies** which deplete fewer than 50% of target cells in vitro. Preferred nd CD4 mAbs deplete fewer than 25% and most. . . .

SUMMARY:

BSUM(11)

For . . . CD4 mAbs may be obtained by conventional techniques for raising mAbs against CD4 and screening and selecting clones with secrete **non-depleting antibodies**. Typically such **antibodies** will be of the IgG.sub.2 class such as rat IgG.sub.2a, mouse IgG.sub.2b or human IgG.sub.2 but human IgG.sub.4 are also. . .

DETDESC:

DETD(4)

In . . . it is shown that YTS177 strongly protects NOD mice from IDDM transferred by diabetic donor spleen cells. YTS177 is a **non-depleting** IgG.sub.2a anti-CD4 rat monoclonal **antibody** which although recognising the same epitope as the depleting IgG.sub.2b monoclonal anti-CD4 YTS191.1 (ECACC 87072282) has a different mode of. . .

DETDESC:

DETD(8)

The doses of the depleting **antibodies** administered in Experiments 3 and 4, although much less than those of the **non-depleting** YTS177, were found previously to deplete animals of virtually all CD4.sup.+ or CD8.sup.+ T cells.

CLAIMS:

CLMS(5)

5. The method of claim 1 which comprises administering more than one dose of **non-depleting** CD4 monoclonal **antibodies**.

CLAIMS:

CLMS(7)

7. The method of claim 1 wherein the administration comprises the use of a saturating amount of at least one **non-depleting** CD4 monoclonal **antibody**.

CLAIMS:

CLMS(8)

8. . . . diabetes mellitus which method comprises administering to a patient in need thereof an effective, non-toxic amount of at least one **non-depleting** CD4 monoclonal **antibody**.

US PAT NO: 5,635,156 [IMAGE AVAILABLE] L2: 3 of 7

SUMMARY:

BSUM(46)

Attempts to induce tolerance to allogeneic bone marrow donor cells using combinations of depleting and **non-depleting** anti-CD4 and CD8

monoclonal **antibodies** (mAb) resulted in only transient tolerance to MHC-compatible combinations (Cobbold et al., 1992, Immunol Rev 129: 165; Qin et al.,. . .

US PAT NO: 5,603,958 [IMAGE AVAILABLE] L2: 4 of 7

DETDESC:

DETD(72)
Two weeks after immunization the mice were bled and the serum was assayed for **antibodies** to the viral proteins (standard Elisa technique employing microtine plates coated with the antigen and a commercial enzyme-conjugated rabbit anti-mouse preparation for detection of mouse **immunoglobulins**). The result shown in table 6 below demonstrates that LT 15 as well as plain saline did not potentiate the **antibody** response to the protein micelles in contrast to the **non-depleted** Quil A preparation.

US PAT NO: 5,514,364 [IMAGE AVAILABLE] L2: 5 of 7

SUMMARY:

BSUM(45)

Attempts to induce tolerance to allogeneic bone marrow donor cells using combinations of depleting and **non-depleting** anti-CD4 and CD8 monoclonal **antibodies** (mAb) resulted in only transient tolerance to MHC-compatible combinations (Cobbold et al., 1992, Immunol Rev 129:165; Qin et al., 1990,. . .

US PAT NO: 5,229,275 [IMAGE AVAILABLE] L2: 6 of 7

DETDESC:

DETD(25)

a) In order to determine the effect of T-cell depletion on the inventive method, systems using depleted and **non-depleted** PBL were used. PBL were collected from donors and separated as described in Example 1. Half of the cells were. . . FIG. 1 shows that the T-cell depleted PBL wells used as controls that contained medium alone produced approximately 10-fold more **immunoglobulin** of each of the isotypes tested.

DETDESC:

DETD(30)

This table shows an increase of 20-40 fold of the **immunoglobulins** produced in supernatants from cultures containing T-cell depleted PBL and the adjuvants 8-MG and IL-4, and 8-MG and IL-6, over the **non-depleted** PBL cultures without adjuvants.

US PAT NO: 4,971,801 [IMAGE AVAILABLE] L2: 7 of 7

DETDESC:

DETD(103)

That . . . or in the absence of natural killer cells, the background or leakage level is below 20% chromium release. With a **non-depleted** cell population, administration of the invention results in clear stimulation of natural killer cell cytotoxicity. Removal of B or T-cells from the population with specific monoclonal **antibodies** does not significantly affect the level of cytotoxicity. Removal of NK cells with monoclonal **antibodies** is shown to eliminate

the cytotoxic effect. Removal of monocytes with monoclonal **antibodies** (not shown) also results in loss of NK cytotoxicity, suggesting that the NK cell is activated by the monocyte-macrophage population.

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L2: 1 of 7

TITLE: Monoclonal antibodies for inducing tolerance
US PAT NO: 5,690,933 [IMAGE AVAILABLE] DATE ISSUED: Nov. 25, 1997
APPL-NO: 08/289,532 DATE FILED: Aug. 12, 1994
FRN-PR. NO: 8912497 FRN FILED: May 31, 1989
FRN-PR. CO: United Kingdom
REL-US-DATA: Continuation of Ser. No. 181,170, Jan. 13, 1994, abandoned, which is a continuation of Ser. No. 47,344, Mar. 29, 1993, abandoned, which is a continuation of Ser. No. 768,868, Jul. 27, 1991, abandoned.

L2: 2 of 7

TITLE: **Non-depleting** CD4-specific monoclonal **antibodies** for the treatment of insulin-dependent diabetes mellitus (IDDM)
US PAT NO: 5,670,150 [IMAGE AVAILABLE] DATE ISSUED: Sep. 23, 1997
APPL-NO: 08/436,843 DATE FILED: May 8, 1995
FRN-PR. NO: 9100741 FRN FILED: Jan. 14, 1991
FRN-PR. CO: United Kingdom
REL-US-DATA: Continuation of Ser. No. 90,203, Dec. 1, 1993, abandoned.

L2: 3 of 7

TITLE: Non-lethal methods for conditioning a recipient for bone marrow transplantation
US PAT NO: 5,635,156 [IMAGE AVAILABLE] DATE ISSUED: Jun. 3, 1997
APPL-NO: 08/337,785 DATE FILED: Nov. 14, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 120,256, Sep. 13, 1993, Pat. No. 5,514,364.

L2: 4 of 7

TITLE: Pharmaceutical carrier
US PAT NO: 5,603,958 [IMAGE AVAILABLE] DATE ISSUED: Feb. 18, 1997
APPL-NO: 08/455,403 DATE FILED: May 31, 1995
FRN-PR. NO: 9101665 FRN FILED: May 31, 1991
FRN-PR. CO: Sweden
REL-US-DATA: Continuation of Ser. No. 142,377, Mar. 30, 1994, abandoned.

L2: 5 of 7

TITLE: Non-lethal methods for conditioning a recipient for bone marrow transplantation
US PAT NO: 5,514,364 [IMAGE AVAILABLE] DATE ISSUED: May 7, 1996
APPL-NO: 08/120,256 DATE FILED: Sep. 13, 1993

L2: 6 of 7

TITLE: In-vitro method for producing antigen-specific human monoclonal antibodies
US PAT NO: 5,229,275 [IMAGE AVAILABLE] DATE ISSUED: Jul. 20, 1993
APPL-NO: 07/514,775 DATE FILED: Apr. 26, 1990

L2: 7 of 7

TITLE: Biologic response modifier
US PAT NO: 4,971,801 [IMAGE AVAILABLE] DATE ISSUED: Nov. 20, 1990
APPL-NO: 07/057,344 DATE FILED: Jun. 2, 1987
REL-US-DATA: Continuation-in-part of Ser. No. 872,131, Jun. 9, 1986, abandoned.

=> d l2 1-7

1. 5,690,933, Nov. 25, 1997, Monoclonal antibodies for inducing tolerance; Stephen Paul Cobbold, et al., 424/144.1, 143.1, 153.1, 154.1, 173.1; 514/11 [IMAGE AVAILABLE]

2. 5,670,150, Sep. 23, 1997, **Non-depleting** CD4-specific monoclonal **antibodies** for the treatment of insulin-dependent diabetes mellitus (IDDM); Anne Cooke, et al., 424/154.1, 143.1, 145.1, 158.1; 530/388.24, 388.75 [IMAGE AVAILABLE]

3. 5,635,156, Jun. 3, 1997, Non-lethal methods for conditioning a recipient for bone marrow transplantation; Suzanne T. Ildstad, 424/1.49, 130.1, 141.1, 152.1, 153.1, 154.1, 178.1, 181.1, 183.1; 600/1; 604/20 [IMAGE AVAILABLE]

4. 5,603,958, Feb. 18, 1997, Pharmaceutical carrier; Bror Morein, et al., 424/489, 484 [IMAGE AVAILABLE]

5. 5,514,364, May 7, 1996, Non-lethal methods for conditioning a recipient for bone marrow transplantation; Suzanne T. Ildstad, 424/1.49, 130.1, 141.1, 152.1, 153.1, 154.1, 178.1, 183.1; 600/1; 604/20 [IMAGE AVAILABLE]

6. 5,229,275, Jul. 20, 1993, In-vitro method for producing antigen-specific human monoclonal antibodies; Diana K. Goroff, 435/70.1; 424/85.2; 435/70.21, 70.4; 530/351, 387.1, 388.1 [IMAGE AVAILABLE]

7. 4,971,801, Nov. 20, 1990, Biologic response modifier; Richard W. Urban, 424/450; 264/4.3; 424/85.2, 282.1; 428/402.2; 436/829; 514/885 [IMAGE AVAILABLE]